REMARKS

Reconsideration of the above-identified application is respectively requested in view of the above amendments and the following remarks is respectfully requested. The Examiner objected to claims 85, 86, 88, and 89 and rejected claims 1, 5, 9, 10, 19, 24, 25, 85-89 for multiple reasons. Claims 1, 5, 9, 10, 14, 19, 24, 25, 85-89 are currently in the case. Claims 1 and 85-89 have been amended. No new matter has been added with these amendments.

Applicant's invention is directed to *inter alia* A medical system for treating a neurodegenerative disorder in a human live patient comprising: (a) an intracranial access device; (b) a mapping means for locating a predetermined location in the brain of a patient, said location comprising cells natively expressing a gene responsible for the neurodegenerative disorder; (c) a deliverable amount of a small interfering RNA capable of inhibiting expression of the gene responsible for the neurodegenerative disorder or a vector encoding said small interfering RNA; and (d) a delivery means for delivering said small interfering RNA or vector encoding said small interfering RNA to said location of the brain of said patient from said intracranial access device through a stereotactically implanted catheter.

Priority

The Examiner has asserted that the priority application (Provisional Patent Application no. 60/429,387) does not support claims directed to medical systems comprising small interfering RNA and thus Applicant is not entitled to the 2002 filing date of Provisional Patent Application no. 60/429,387. The Examiner does acknowledge, however, that Provisional Patent Application no. 60/444,614, filed on February 3, 2003 provides adequate support for claims drawn to medical systems comprising small interfering RNA. Accordingly, Applicant withdraws the claim to domestic priority to Provisional Patent Application no. 60/429,387 filed on November 26, 2002, but maintain the claim for domestic priority to Provisional Patent Application no. 60/444,614, filed on February 3, 2003 under 35 U.S.C. § 119(e).

Claim Objections (new)

The Examiner objected to claims 85, 86, 88, and 89 because of grammatical informalities. Applicant has amended the objected claims in accordance with the Examiner's request. Accordingly, Applicant respectfully requests that the Examiner withdraw these objections.

Rejection Under 35 U.S.C. § 112 ¶2

The Examiner rejected claims 87-89 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 87 has been amended in accordance with the Examiner's request.

Claim 88 has been rejected because, according to the Examiner's assertion, the phrase "sufficient length" is a relative term. Applicant draws the Examiner attention to paragraph [0060]. The term "sufficient length" is defined in paragraph [0060] of the specification as "greater than or equal to 15 nucleotides that is of a length great enough to provide the intended function under the expected conditions." Applicant respectfully submits that the person of the ordinary skill in the art will be able to understand this definition, and Applicant has herewith amended claim 88 to recite this language. Thus Applicant respectfully requests that this ground of rejection be withdrawn.

The Examiner rejected claim 89 because, in his opinion, the disclosure would not inform a person of ordinary skill in the art about the meaning of the term "stably interact," as used in the claim. Contrary to the Examiner's assertion, Applicant respectively submits that the instant specification discloses the meaning of the phrase "stably interact" and respectfully draws the Examiner's attention to paragraph [0060] which specifically recites as follows:

> The small interfering RNA sequence needs to be of sufficient length to bring the small interfering RNA and target RNA together through complementary base-pairing interactions. The small interfering RNA of the invention may be of varying lengths. The length of the small interfering RNA is preferably greater than or equal to ten nucleotides and of sufficient length to stably interact with the target RNA; specifically 15-30 nucleotides; more specifically any integer between 15 and 30 nucleotides, such as 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30. By "sufficient length" is meant an

> oligonucleotide of greater than or equal to 15 nucleotides that is of a length great enough to provide the intended function under the expected condition. By "stably interact" is meant interaction of the small interfering RNA with target nucleic acid (e.g., by forming hydrogen bonds with complementary nucleotides in the target under physiological conditions).

Applicant respectfully submits that the person of the ordinary skill in the art would be able to understand this definition of the term "stably interact" to mean that the small interfering RNA sequences of the instant invention are between 15 and 30 nucleotides in length which is of sufficient length to bring the small interfering RNA and target RNA together through complementary base-pairing interactions.

Provisional obviousness-type double patenting rejection

The Examiner further rejected claims 1, 9-15, 19, and 25 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 7, 8, 16, 17, and 29 of a co-pending application No. 10/962,732.

MPEP § 804(I)(B)(1) recites as follows:

> [i]f a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer."

Applicant respectfully notes that the instant application was filed on 11.25.2003, while application No. 10/962,732 was filed later. Therefore, the instant application is the earlier-filed application of the two applications. Applicant further notes that as of June 13, 2006, no action on merits have been taken regarding the later-filed application No. 10/962,732.

Accordingly, without making any admissions or agreeing with the Examiner, Applicant respectfully requests postponement of any action on this ground of rejection until this is the only ground for rejection of either claims 1, 9-15, 19, and 25 of the instant application or claims 7, 8, 16, 17, and 29 of a co-pending application No. 10/962,732.

Rejection on the basis of 35 U.S.C. §103

The Examiner has rejected claim 1 under 35 U.S.C. § 103 as being unpatentable over Xia et al. (2002) *Nature* 20:1006–1010; Driscoll et al. (WO 01/49844); Paxinos et al. (2001) *The Mouse Brain in Stereotaxic Coordinates.* Academic Press, 2nd Ed; and Cahill et al. (1995) *Atlas of Human Cross-sectional Anatomy,* Wiley-Liss, 3rd ed.

Xia et. al. discloses a method of inhibiting expression of a transgene using a syringe to inject a vector comprising a siRNA sequence less than 30 nucleotides in length into the striatum of transgenic mice.

Contrary to Xia, Driscoll discloses that the siRNA should be between 20 nucleotides and over 1,000 nucleotides, and the siRNA is expressed from a vector to suppress expression of GFP in *C. elegans*. Applicant respectfully notes that while Driscoll provides some teaching as to how to make vectors associated with neurodegenerative disorders, Applicant could not find any particular teaching of delivery systems and how to deliver these molecules to particular targets, or any suggestion of the usefulness to consider these factors. Driscoll does not teach or suggests the need to have an intracranial access device, a mapping means, or use of the device with the mapping means to direct delivery of the siRNA to predetermined locations of the brain.

Paxinos and Cahill disclose anatomical atlases of mouse and human brains, respectively, which the Examiner interprets as mapping means. At best, these references disclose laundry lists of brain structures and their relative locations. These references do not teach or suggest which brain structures, let alone any brain structure that are important for siRNA therapy of the neurodegenerative diseases, nor do they disclose which structures endogenously express genes responsible for the neurodegenerative disorders.

MPEP § 2143.03 states that to establish the prima facie case of obviousness of a claimed invention, all the claim limitations must be taught or suggested.

Applicant respectfully notes that the combination of the references cited above do not teach or suggest <u>all</u> limitations of the newly amended claim 1. First, claim 1, as currently amended, is drawn to neurodegenerative diseases in <u>humans</u>. Second, the combination of the cited references does not disclose a stereotactically <u>implanted</u> catheter (i.e., a device providing access to the cranium even between deliveries of the siRNA

therapy). Instead, the references disclose a direct injection by syringe, which is removed after the injection is complete. Third, these references neither teach nor suggest the use of an siRNA therapy for inhibiting expression of an endogenously expressed gene.

For at least these reasons, Applicant respectfully requests that the Examiner withdraw this rejection.

Rejection on the basis of 35 U.S.C. §103

The Examiner further rejected claims 1, 5, 9, 10, 17, 24, and 25 under 35 U.S.C. § 103(a) as being unpatentable over Xia et al. (2002); Driscoll et al.; Paxinos et al (200); and Cahill et al, and further in view of Whitesell et al. (1993); Davidson (2004); and Matilla et al (1998).

Applicant respectfully submits that the Examiner's reliance on Xia, Driscoll, Paxinos, and Cahill to make obvious Applicant's claimed invention is misplaced and has already been discussed above. The Examiner's further reliance on additional secondary references does not cure the infirmities in Examiner's argument.

The Examiner cites Whitesell for teaching a system for intraventricular administration of radioactively or fluorescently labeled antisense oligonucleotides into rats (pages 4665-6). The Examiner asserts that Whitsell discloses that the rats had a 22-gauge steel catheter stereotactically implanted in the lateral ventricle through which labeled antisense oligonucleotides were injected by bolus injection with a Hamilton syringe or continuous injection using a mini-osmotic pump (page 4666). The Examiner further asserts that because the oligonucleotides were fluorescently labeled, Whitesell is also able to determine, or map the location and distribution of the perfused oligos. Thus, the Examiner asserts, the oligonucleotides themselves, by virtue of their label, comprises a mapping means.

The Applicants respectfully disagree with the Examiner's interpretation of Whitesell. Whitesell reports that its study supports the feasibility of continuously perfusing the CNS with therapeutic concentrations of intact antisense oligonucleotides, and the possibility of using such therapeutics to target leptomeninigeal and intraparenchymal disease processes (page 4669). Applicant respectfully submits that the instantly amended claims are directed to siRNA and not antisense. The Examiner has already recognized that siRNA and antisense are different technologies. A second reason that Whitsell is inapposite to the

instant invention is that the oligonucleotides used in Whitesell are not the mapping means disclosed in pending claim 1. Claim 1 discloses mapping means to locate a predetermined location in a brain. Thus, the location in the brain must be determined before the administration of the siRNA treatment, not during or after such treatment. Clearly, labeled oligonucleotides disclosed in Whitesell are incapable of mapping a location in the brain prior to being administered inside the brain. Accordingly, the combination of the references discussed above and Whitesell does not add anything to the anatomical atlases of mouse and human brains disclosed in Paxinos and Cahill, whose shortcomings have been discussed above.

Further, Whitesell discloses injection of the oligonucleotides into lateral ventricles. Such injection results in distribution of the oligonucleotides primarily into glial cells, vascular cells, and structures adjacent to the ventricles, which shows only a limited penetration of the oligonucleotides into parenchymal tissues of brain. There is no teaching or suggestion in Whitesell that ssDNA is delivered into neurons.

Applicants further respectfully submit that Whitesell does not suggest that the same technique would be useful for injecting much longer viral vectors comprising the siRNAs. The fact that phosphorothioated ssDNA isn't so rapidly degraded in CSF does not make it reasonably predictable that dsRNA wouldn't be rapidly degraded by enzymes in the CSF, nor that double-stranded DNA expression cassettes would penetrate brain tissue from the CSF in the manner that Whitesell reported for their short oligonucleotides of ssDNA. Most importantly, it is unclear whether the administration of Applicant's siRNA by the method disclosed in Whitesell would result in the inhibition of expression of an endogenously expressed gene involved in a neurodegenerative disorder.

Davidson discloses a possibility of treating neurodegenerative diseases, including spinocerebellar ataxia (SCA), by an siRNA therapy. However, Davidson does not disclose or suggest intracranial infusion of the specific siRNAs, let alone infusion of those siRNAs into the brain structures for inhibition of expression of SCA genes responsible for a neurodegenerative disease. Thus, Davidson does cure the deficiencies of the combination of Xia, Driscoll, Paxinos, Cahill and Whitesell.

The Examiner cites Matilla for providing the motivation to create systems for delivering SCA1 targeting siRNAs into the brains of mice or rats arguing that Matilla

discloses that SCA1 has a genetic basis involving the expression of a mutant or toxic form of an SCA1 gene in Purkinje cells of the brain causing loss of these cells and an ataxic phenotype (page 5508). Matilla only discloses that knocking out SCA1 gene function from embryonic conception does not cause an ataxic phenotype in the developing or adult animal, indicating that the SCA1 disease in humans is not due to a loss of the function of the SCA1 gene or ataxin-1 protein. Matilla does not teach or suggest suppression of the expression of the SCA1 gene in patients as a means of treating the disease. No suggestion is provided to explore siRNA technology as a means for doing so. Finally, no suggestion is provided to administer siRNA in the areas endogenously expressing SCA-1.

Accordingly, the combination of the references cited by the Examiner will not teach or suggest all limitations of claim 1 in its currently amended form. For at least this reason, Applicant respectfully requests that the Examiner withdraw this ground for rejection of claim 1.

Claims 5, 9, 10, 19, 24, 25, 85-87, and 89 depend on claim 1 and thus include all limitations of claim 1. Since the combination of references suggested by the Examiner does not make obvious currently amended claim 1, such a combination of references does not make obvious the claims dependent from claim 1. MPEP § 2143.03. For at least these reasons, Applicant respectfully requests that the Examiner withdraw his rejection of claims 1, 5, 9, 10, 19, 24, 25, 85-87, and 89 under 35 U.S.C. § 103(a).

Applicants respectfully submit that the pending claims are valid and favorable reconsideration and allowance are earnestly solicited. If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that the Examiner telephone Applicant's attorney at (609) 844-3020 to discuss any additional rejections.

The USPTO is authorized to charge Deposit Account No. 50-1943 for any charges in connection with this matter.

Respectfully submitted,

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